303

Sodium Intake and Health Outcomes: A Systematic Review of Systematic Reviews

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Introduction

- Excessive sodium consumption has been associated with adverse health outcomes, including hypertension, cardiovascular disease, renal disorders, and mortality[1-4]
- In the United States, 2300 mg sodium, the daily intake upper limit recommended by multiple authoritative bodies, including the National Academy of Sciences (NAS), Institute of Medicine (IOM), US Food and Drug Administration (FDA), and US Department of Agriculture (USDA), is exceeded by an average of ~1100 mg/day through diet alone[3-7]
- Chronic use of certain medications, such as effervescent paracetamol, can lead to substantially higher than normal sodium consumption; some narcolepsy medications contain up to 1640 mg sodium per 9 g nightly dose[8-10]
- As numerous systematic reviews (SRs) have been performed on the impact of sodium consumption on health outcomes, a summary of the evidence to date is needed on the relationship between different levels of sodium intake and clinical outcomes

Objective

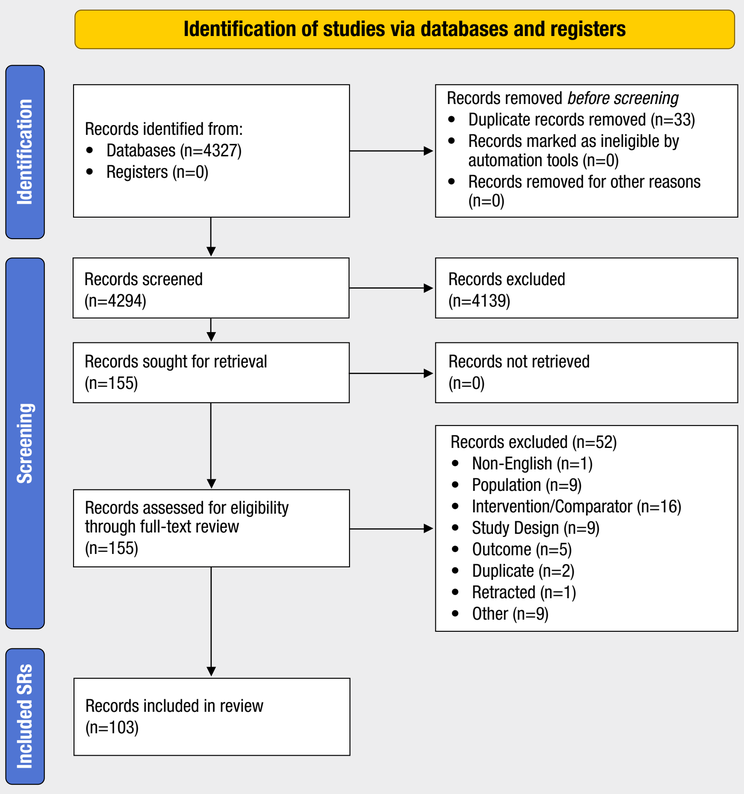
- To identify and synthesize the clinical evidence on the relationship between sodium intake and adverse health outcomes

Methods

- An SR of the literature was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[11] and the *Cochrane Handbook for Systematic Reviews of Interventions*[12]
- Ovid Medline, Embase, and EBMR (Evidence-Based Medicine Reviews) databases were searched for English-language records published between 1/1/2012 and 2/28/2023
- The systematic search was performed by a senior information specialist. Another information specialist used the PRESS (Peer Review of Electronic Search Strategies) checklist to peer-review the search strategies,[13] and DistillerSR (DistillerSR Inc., Ottawa, Canada) was used to perform study selection in parallel
- SRs evaluating the relationship between different levels of sodium intake/replacement and health outcomes (eg, cardiovascular disease, hypertension, stroke, myocardial infarction, heart failure, edema, gastrointestinal tumors, neurologic disorders, mortality) were included in the review, based on prespecified PICOS (population, intervention, comparator, outcomes, study design) eligibility criteria
- This review focused primarily on SRs reporting meta-analyses. Where multiple meta-analyses existed for a health outcome, the most comprehensive review (MCR) for that outcome was identified based on study objective, eligibility criteria, number of included studies, methodological quality per AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) evaluation, and whether measurable differences between different sodium intake levels had been evaluated

Results

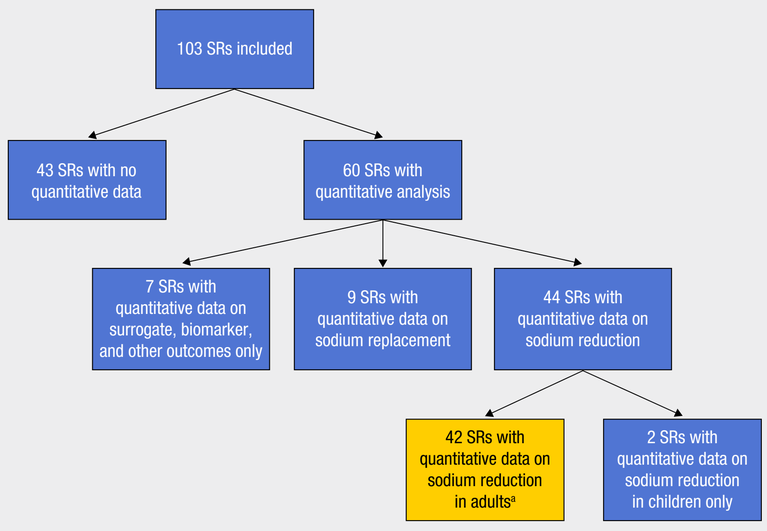
Figure 1. PRISMA Diagram of Study Identification and Selection



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR, systematic review.

- Of 4327 publications identified through database searches and screened, 103 SRs were included in this review

Figure 2. This SR Captured 42 SRs With Quantitative Data on Sodium Reduction in Adults



[a]SRs selected were the most comprehensive for outcomes with multiple meta-analyses.
SR, systematic review.

- The Results section of this poster focuses on the 42 SRs that performed meta-analyses on health outcomes for sodium reduction in adults
- Most of the identified SRs were of critically low quality, as per AMSTAR 2 assessment. The most common reasons for that assessment included:
  - No list of excluded studies and reasons for exclusion
  - No explanation that review methods were defined pre-study
  - Inadequate justification for significant protocol deviations
  - Failure to account for risk of bias assessment results in interpreting study findings
- In total, 12 health outcomes were the subject of multiple meta-analyses, the results of which were informed by MCR per outcome; 12 health outcomes were the subject of a single meta-analysis

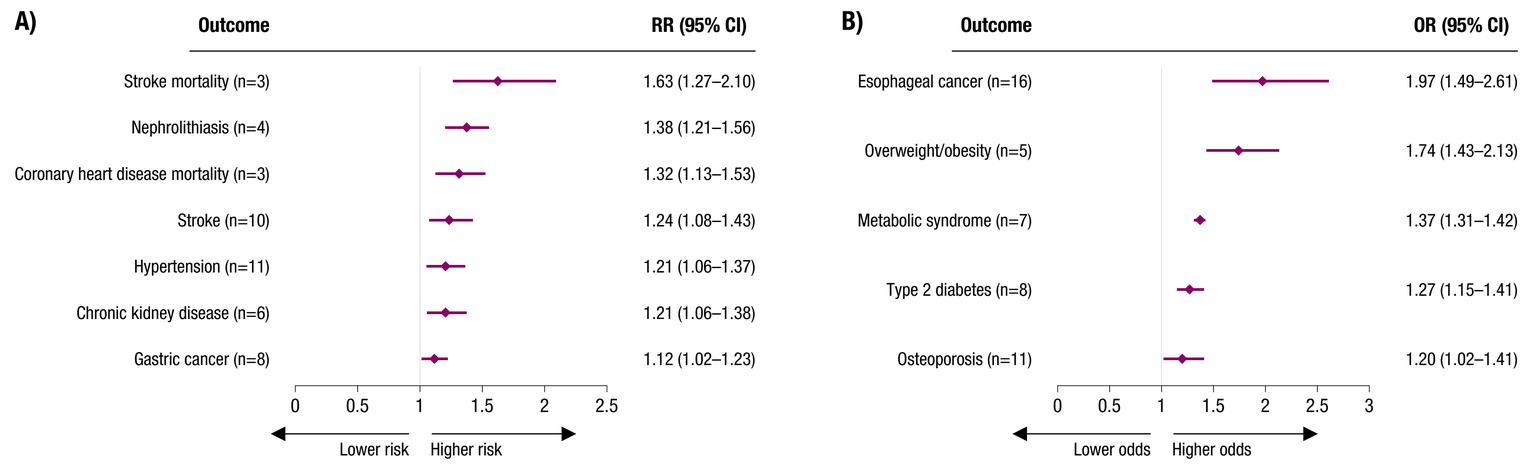
Table 1. Lower Sodium Intake Was Significantly Associated With Blood Pressure Decreases in Adults[14,15]

Study	Type of Studies Included in SR	Studies Included, n	Exposure/Comparison	Outcome	Mean Difference, mm Hg (95% CI)
Aburto et al, 2013[14]	RCTs, quasi-RTs, nRCTs, and prospective, observational cohort studies	36	Lower sodium intake (≥40 mmol/day difference)	Systolic BP	–3.39 (–4.31, –2.46)
				Diastolic BP	–1.54 (–2.11, –0.98)
Graudal et al, 2012[15]	RCTs	23	Lower sodium intake (mean, 71 mmol/day) vs higher sodium intake[a] (mean, 196 mmol/day)	Mean BP	–3.56 (–4.07, –3.06)

[a]In hypertensive White population.
BP, blood pressure; CI, confidence interval; nRCT, non–randomized controlled trial; RCT, randomized controlled trial; RT, randomized trial; SR, systematic review.

- Overall, 5 of 18 SRs reported ≥1 meta-analysis finding a statistically significant association between sodium intake and mean blood pressure
- Relative to higher sodium intake, lower intake was significantly associated with reductions in systolic, diastolic, and mean blood pressure[14,15]

Figure 3. Higher Sodium Intake Was Significantly Associated With Adverse Health Outcomes for (A) RRs and (B) ORs[14,16-24]



CI, confidence interval; n, number of studies included in meta-analysis; OR, odds ratio; RR, risk ratio (relative risk).

- Relative to lower sodium intake, higher sodium intake was significantly associated with increased risk or odds of unfavorable health outcomes in adults[14,16-24]
- For esophageal cancer, the risk associated with sodium intake was higher for esophageal squamous cell carcinoma relative to esophageal adenocarcinoma (odds ratio [OR], 2.28; 95% confidence interval [95% CI], 1.65–3.15), for study participants in developing countries relative to participants in developed countries (OR, 2.24; 95% CI, 1.68–3.00), and for salted food relative to sodium (both types of dietary salt; OR, 2.46; 95% CI, 1.81–3.35), indicating that type of esophageal cancer, geographic location, and type of dietary salt significantly moderated the association between sodium intake and risk of esophageal cancer[16]
- For overweight/obesity, subgroup analyses showed the risk associated with sodium intake was higher for males than females (OR, 1.74; 95% CI, 1.38–2.18)[17]
- Subgroup analyses found a significant association between sodium intake and chronic kidney disease for <10 years exposure duration (OR, 1.32; 95% CI, 1.02–1.70), for non-US subgroups (OR, 1.28; 95% CI, 1.04–1.58), and for study participants with baseline glomerular filtration rate (GFR) ≤89.9 mL/min/1.73m^2 (OR, 1.34; 95% CI, 1.08–1.67); for >10 years exposure duration, US subgroups, and baseline GFR ≥90 mL/min/1.73m^2, the association was found to be nonsignificant, though in the expected direction (OR, 1.14 [95% CI, 0.98–1.31]; OR, 1.10 [95% CI, 0.98–1.24]; OR, 1.08 [95% CI, 0.94–1.25], respectively)

Table 2. Results for the Association Between Sodium Intake and Adverse Health Outcome, by SR[14,16-24]

SR	Type of Studies Included	Studies Included, n	Exposure/Comparison	Outcome	Mean Difference (mm Hg) (95% CI)
Aburto et al, 2013[14]	RCTs, quasi-RTs, nRCTs, and prospective, observational cohort studies	10	Higher sodium intake (difference of ≥40 mmol/day and risk of stroke, all events)	Stroke	RR: 1.24 (1.08–1.43)
		3	Higher sodium intake (difference of ≥40 mmol/day)	Stroke mortality	RR: 1.63 (1.27–2.10)
		3	Higher sodium intake (difference of ≥40 mmol/day)	Coronary heart disease mortality	RR: 1.32 (1.13–1.53)
Fang et al, 2015[24]	Prospective cohort studies	8	5 g/day increase in sodium intake	Gastric cancer	RR: 1.12 (1.02–1.23)
Fatahi et al, 2018[23]	Cross-sectional, cohort studies	11	Difference in outcomes caused by increase in sodium intake	Osteoporosis	OR: 1.20 (1.02–1.41)
Soltani et al, 2019[19]	Observational studies	7	Highest vs lowest sodium levels	Metabolic syndrome	OR: 1.37 (1.31–1.42)
Lin et al, 2020[18]	Observational studies	4	Highest level of sodium exposure vs lowest level of sodium exposure	Nephrolithiasis	RR: 1.38 (1.21–1.56)
Banda et al, 2020[16]	Observational (cohort and case–control studies)	16	Highest level of dietary salt vs lowest level of dietary salt in case–control studies	Esophageal cancer	OR: 1.97 (1.49–2.61)
Grimes et al, 2021[17]	Cross-sectional studies, longitudinal studies, RCTs	5	Average difference between highest and lowest n-tile was 162 mmol/day of sodium (salt, 4.0 g/day)	Overweight and obesity	OR: 1.74 (1.43–2.13)
Kelly et al, 2021[22]	Cohort studies, prospective or retrospective	6	High salt intake, ranging from ≥9.88 g/day to 16.27 g/day (sodium, ≥172 mmol/day to 283 mmol/day), vs lower sodium intake	Chronic kidney disease	RR: 1.21 (1.06–1.38)
Kolahdouz-Mohammadi et al, 2021[20]	Observational (cross-sectional, case–control, or cohort studies)	8	Highest urinary sodium vs lowest urinary sodium categories	Type 2 diabetes	OR: 1.27 (1.15–1.41)
Filippini et al, 2022[21]	Observational studies (cohort studies)	11	Association between sodium intake of 6 g/day and incidence of hypertension, compared with 2 g/day	Hypertension	RR: 1.21 (1.06–1.37)

CI, confidence interval; nRCT, non–randomized controlled trial; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio (relative risk); RT, randomized trial; SR, systematic review.

- Overall, 10 SRs reported a significant association between sodium intake and adverse health outcomes in adults[14,16-24]
- Relative to lower sodium intake, higher sodium intake was significantly associated with higher risk or odds of stroke mortality (relative risk [RR], 1.63; 95% CI, 1.27–2.10), nephrolithiasis (RR, 1.38; 95% CI, 1.21–1.56), metabolic syndrome (OR, 1.37; 95% CI, 1.31–1.42), coronary heart disease mortality (RR, 1.32; 95% CI, 1.13–1.53), type 2 diabetes (OR, 1.27; 95% CI, 1.15–1.41), stroke (RR, 1.24; 95% CI, 1.08–1.43), hypertension (RR, 1.21; 95% CI, 1.06–1.37), osteoporosis (OR, 1.20; 95% CI, 1.02–1.41), and gastric cancer (RR, 1.12; 95% CI, 1.02–1.23)[14,18-21,23,24]
- Higher sodium intake was numerically associated with ischemic stroke (RR, 1.14; 95% CI, 1.00–1.27), composite cardiovascular events (RR, 1.12; 95% CI, 0.93–1.34), cardiovascular disease mortality (RR, 1.08; 95% CI, 0.87–1.33), combined cardiovascular disease morbidity and mortality (RR, 1.08; 95% CI, 0.78–1.47), all-cause mortality (RR, 1.06; 95% CI, 0.94–1.20), coronary heart disease (RR, 1.04; 95% CI, 0.86–1.24), heart failure (rate ratio, 0.99; 95% CI, 0.89–1.10), albuminuria (OR, 1.01; 95% CI, 0.89–1.14), and kidney function in diabetes (mean difference, –1.87/mL/min/1.73m^2; 95% CI, –5.05 to 1.31)[14,22,25-27]
- Sensitivity analyses performed for the outcomes of stroke, stroke mortality, coronary heart disease mortality, and nephrolithiasis showed that removal of studies with high risk of confounding had minimal impact on the results

Conclusions

- Relative to lower levels, higher levels of sodium intake in adults significantly increase the risk or odds of adverse health outcomes, ranging from certain gastrointestinal cancers to metabolic, renal, and cardiovascular conditions or events, including mortality[14,16-24]
- The findings support the current recommendation by the US FDA, World Health Organization, and other health organizations to maintain sodium intake under the recommended daily limit of 2300 mg in order to protect short- and long-term health[5,28]
- As even modest reductions can lower the risk of adverse health outcomes,[14,15] patients with narcolepsy may benefit from medications with low sodium content. Minimizing chronic exposure to excess sodium may be particularly advantageous for people with narcolepsy, who have a higher prevalence of cardiovascular disease and other comorbidities and are at increased risk of new-onset cardiovascular events, compared with people without narcolepsy[9,29]

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